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Osteoporosis Prevention in Women –Exercise and Non-pharmacological Approaches

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Abstract

The objective of the review was to provide non-pharmacological approaches to improve bone health and prevent osteoporosis in women. The specific objectives are

1) To recommend approaches to build strong bone or peak bone mass in women with regular exercise training or sports participation, and

2) To provide better guidelines for non-pharmacological supplement use to prevent or treat osteoporosis. Consistently high-impact exercise training and high-intensity resistance training provide different site-specific effects in both upper and lower limbs. Bone quality and bending strength can be improved if the mechanical stimulus is induced by short increments rather than over long periods of time.

The consensus among bone clinicians and researchers as to the potential osteogenic exercise stimuli include

1) Impact-load activities should be at high magnitude and low repetitions,

2) Long-term mechanical loading should be separated into short bouts of work- rest intervals, and

3) The strain or load imposed on the skeleton should be distributed throughout the bone structure, involving multiple directions and be progressive in nature. For building strong bone or peak bone mass during the growing years for teenagers or young adults the logical approach is to engage in regular exercise training or sports participation because these types of musculoskeletal loading activities are relatively safe and without side effects especially when we begin engagement in regular exercise training/sports participation at a younger age (e.g. with club sports) and continue to adulthood and old age (e.g. with supervision by qualified professional personal trainers). Discussion also includes possible mechanisms of musculoskeletal impact loading exercise training and sports participation on enhancing or maintaining bone strength and bone mineral density as well as non-pharmacological supplements such as calcium and vitamin D to prevent osteoporosis.

Keywords: bone health, bone resorption and formation process, exercise training modality and bone health, sport participation and bone health, non-pharmacological and supplements

Introduction

Osteoporosis is a loss of bone mass with a deterioration of bone quality and increased fracture risk.[1] The WHO criteria for determining osteoporosis is a reduction in bone mineral density (BMD) of 2.5 standard deviation (SD) below the average value for young healthy adults assessed by dual-energy X-ray absorptiometry (DXA).[1] Thus, osteoporosis is considered a silent skeletal disease characterized by increased bone resorption without adequate compensating formation of new bone.[2,3] Osteoporosis can occur at any age and in both genders and is typically an age-related disease that more frequently affects women than men.[2] There is a worldwide epidemic associated with increased fracture risk leading to morbidity, mortality and socioeconomic burden. It is estimated that 47% of women and 22% of men over the age of 50 years will sustain an osteoporotic fracture in their remaining life time.[4] In the U.S. there were approximately 10 million women who had osteoporosis and 2.3 million fragility fractures in 2020.[5] Among the total fragility fractures, 27% are vertebral fractures, 19% wrist fractures, 14% hip fractures, 7% pelvic fractures and 33% other type of fractures.[4] The total annual expense of providing direct care of osteoporosis related fractures was estimated at US $17 million.[6]

The proposed solutions for containing the cost of osteoporosis related fracture include

1) Better implementation of clinical guidelines for the disease treatment and management options which include diagnosis and prevention and
2) Building strong bone or peak bone mass during the growing years as teenagers or young adults.[7]

Physiology of Bone

Skeleton is composed of 80% cortical (or compact) bone and 20% trabecular (or cancellous) bone, and the cortical bone is typically found in the shafts of long bones and the vertebral end plates and has relatively low metabolic activity.[8] Structurally, cortical bones consist of solid outer casing that provides the shape and strength of the bones.[8] Trabecular bone is located in the vertebral bodies, pelvis, and the proximal and distal ends of long bones and consists of plates, arches and struts with bone marrow in the spaces between the structures as well as contains hematopoietic or fatty marrow which has a high metabolic rate per unit of volume.[8] Because of these differences between cortical and trabecular bones the rate of change in bone mass and density is greater at sites with predominantly trabecular bone.[8]

The major cellular components in bone are osteocytes which represent more than 95% of all bone cells and are 20-fold more than osteoblast cells.[9] The characteristic feature of osteoclasts is their unique capacity to dissolve them in eralized collagen matrix in bone, i.e., crystalline hydroxyapatite, by targeted secretion of hydrochloric acid (HCl) into the extracellular resorption lacunain bone tissue.[9] The organic matrix of bones is degraded by enzymes like cathepsin K and the degradation products are transcytosed through the cell for secretion.[9]

A. Major Pathways in Bone Remodeling.

During bone remodeling one of the major pathways involved in bone homeostasis includes the RANKL/RANK/OPG system *(RANKL "receptor activator of nuclear factor kB ligand";RANK, "receptor activator of nuclear factor kB"; OPG, "osteoprotegerin"),* which produces signals maintaining the balance between bone resorption and formation.[10] Osteoblasts (e.g., bone formation cells) release a protein called osteoprotegerin (OPG) that can attach to the RANKL and act as RANKL's natural inhibitor.[11] This process is balanced in premenopausal women; however, in postmenopausal women, a drop in estrogen causes an increase in RANKL expression, which bypasses OPG and results in augmented binding with RANK, resulting in an increase in osteoclast activity and bone resorption, which ultimately results in osteoporosis.[12] It has been reported that abnormalities of the RANKL/RANK/OPG system have been implicated in the pathogenesis of postmenopausal osteoporosis.[13] Thus, osteoporosis occurs in older women more than premenopausal women because of the estrogen effect during menopause.[10] The possible mechanisms of estrogen effect on bone include

1) estrogen acts directly via suppression of osteocyte receptors that activate osteoclastic activity, and
2) estrogen has an anti-oxidant effect on osteocytes.

Note that estrogen plays an important role in the mechanical adaptation to loading in girls, particularly prior to the end of puberty, with the interval around Tanner stages II-III or around the age of menarche, because in adolescent girls during menarche their skeleton's ability to adapt to mechanical loading via physical activity or exercise training is greatly enhanced when estrogen levels are high.[14,15] The highlighted mechanosensitivity of peripuberty implies a potential role for the sex steroids in mechanical adaptation in osteogenesis.[14] During the early phase of bone remodeling period, in the cortical bone tunnels are created by osteoclastic activity and are thought to be the beginning of bone resorption period that lasts about 30 days.[16,17] Parathyroid hormone activates osteoblasts by transforming preosteoclasts into mature osteoclasts.[9,16] It is estimated that the lifespan of osteoclast cells is only a few days, due to preprogrammed cell death known as apoptosis.[16,17] The osteoblast cells are found in bone marrow's stem cells and are the cells responsible for bone formation. After osteoblast cells fill the eroded bone surface the osteoclast will

1) be embedded in the bone as osteocytes,
2) be transformed into inactive surface osteoclasts known as lining cells, or
3) have undergone preprogrammed cell death (apoptosis).[16,17] The dying or dead osteocytes serve as initiators of targeted bone remodeling in response to physiologic or excessive strain to prevent the accumulation of micro-damage.[16]

B. Bone Turnover (Remodeling) Process.

Manolagas[18] reported that the sequence of events in bone turn over include

1) bone remodeling process leading to the resorption of the micro-crack in the bone matrix and surrounding old, mineralized bone, and
2) replacing this damaged or eroded bone with newly formed bone with more favorable properties. This new bone tissue is also known as lamellar bone. This process of bone remodeling is estimated to last for 90 days.[18]

Thus, healthy human bones are active dynamic tissues undergoing constant growth via the process of bone modeling and remodeling.

Physiological Response in Bone Formation and Resorption.

The rate of bone formation and loss depends on stage of life and genetic factors as well as intensity and frequency of musculoskeletal impact loading on bone induced by physical activities of daily living. In children and adolescents, bone grows from proliferation of cartilage at the growth plates to subsequent calcification. At this growth stage, the "modeling" of bone tissue involves changing in the shape or axis length of bone in response to mechanical and physiological stress or loading. This phase of bone "modeling" ceases after age 20.[7,19,20] The optimal period of life to begin exercise training or sports participation to attain peak bone mass for both girls and boys is during the growing adolescent years. During growth, the human skeleton undergoes continuous bone deposition and resorption, with a net increase in bone size.[7,19,20] Bone modeling continues until epiphyseal fusion by the end of second decade of life.[19,21] Note that the plateau when age-related bone growth is no longer positive is often referred to as peak bone mass.[20]

In young adulthood, bone undergoes a process of repeated "remodeling" in which old and eroded bone is removed and new bone is synthesized.[17,19] Accordingly, bone "remodeling" continues throughout adulthood, which is the human body undergoes continuous bone resorption and formation resulting in a net gain of bone tissue, until the balance of bone formation and resorption ceases. Note that when the resorption of bone tissue is greater than bone formation, osteoporosis begins.[17,19]

In middle-age and older adult, bone remodeling results in gaining new periosteal bone (with a small gain in endosteal bone) in accordance with Wolff's Law of bone modeling.[22] Wolff's law describes bone change in the shape or alignment and function is followed by certain changes in their internal architecture and secondary changes in their external conformation.[22] As described by Wolff's Law, "bone modeling is to efficiently meet the needs of mechanical loads using the least amount of bone tissue to maintain strength".[15,23] The result is to gain new periosteal bone with little gain in endosteal bone.

A. Biochemical Signaling Factor of Nitric Oxide in Bone Formation.

The mechanical adaptation of bone starts with mechanotransduction. This process resides in bone cells which perceive a mechanical stimulus and translate it into a biochemical response.[24] Mechanotransduction is followed by the signaling from the sensor cells (osteocytes) to the effector cells (osteoblasts or osteoclasts), resulting in bone formation or resorption[22] In this case the signaling factor is nitric oxide (NO) and NO plays a critical role in bone mass regulation.[25-28] During exercise training, the release of NO from the cell body is a known mediator of the response of osteocytes to mechanical loading.[24,29,30] NO has been shown to have many osteogenic effects on bone, it reduces osteoclast motility and increases some cytokine actions on osteoblasts.[29,30] as well as that NO inhibits osteoclasts.[31] and stimulates osteoblasts differentiation.[32] Inducible NOS (iNOS) is a calcium-independent inducible enzyme that is upregulated and activate during inflammatory processes and is responsible for the production of very high amount of NO.[24] Once activated, iNOS is capable of generating sustained high levels of NO locally over many hours.[33] In a postmenopause exercise training study, female subjects consumed 13 mmol NO in the form of beetroot juice for 2 days prior to experimental visits and 2 hours prior to testing Hogwoodetal.[34] found that NO^- supplementation combined with high-intensity exercise improved vascular peak flow-mediated dilation in estrogen-deficient post menopause females compared with non-exercise control females. It has also been reported that NO has an estrogen-like effect on bone formation and can in part replace the beneficial effect of estrogen in bone.[35,36] Thus, NO can inhibit bone loss and was indicated for the prevention and treatment of osteoporosis in adults.[24]

B. Bone Formation and Resorption–the Fluid-Filled Spaces Surrounding Osteocytes and Canalicular Processes Mechanism.

In humans, bone mass reaches its peakand remains relatively stable before age20[7,19,20] and bone loss begins during the onset of menopause in women or reaching the age of 70 years in men [19,20] as well as during physical inactivity and bed rest.[37] One of the proposed signals that allow bone to adapt to its mechanical environment involve strain- mediated intercellular fluid movement with in the fluid-filled spaces surrounding osteocytes and canalicular processes, creating fluid shear stresses on the osteocytes.[38,39] It has been reported that the fluid movement can only be moved through osteocytes by cyclic mechanical loading or stress, and the shear stresses generated on osteocytes are proportional to the rate of loading.[38] Regarding dynamic musculoskeletal impact loading activity during exercise training, Turner and Robling[40] reported that this type of impact loading activity creates hydrostatic pressure gradients within bones' fluid-filled lacunar-canalicular network, generating shear stresses on the plasma members of resident osteocytes and increasing osteoblasts activity. Thus, strain-derived fluid flow of interstitial fluid through the lacunar-canalicular network system seems to mechanically activate the osteocytes and also ensures transport of signaling molecules, nutrients, and waste products.[24,37,41] In other words, increases in blood flow and vascular shear stress during exercise may facilitate advantages bone modeling responses that are mediated by endothelium-derived signaling molecules.[41] Also, mechanical loading of bone during exercise delivers compressive forces to distant regions of the bone such that bone interstitial fluid can flow from regions of high fluid pressure to regions of low fluid pressure, and such fluid flow has been suggested to inhibit osteoclastic and stimulate osteoblastic activities.[39,42,43] Thus, the mechanotransduction, followed by the signaling from the osteocytes to osteoblasts or osteoclasts, resulting in bone formation or resorption.[40,44] Burr et al.[38] suggested that musculoskeletal loading activities involving higher loading rates are more effective for increasing bone formation, even the duration of the activity is short. Note that very little mechanical stimulation is required to initiate an adaptive response in bone. For example, Rubin and Lanyon[45] showed in animal experiment that 36 cycles/day at physiologic strain magnitudes (2000 µ€ in compression) were as effective in promoting bone formation as 1800cycles/day at the same strain magnitude. Note that mechanical loading of bone shows a potent osteogenic stimulus to bone cells, and that bone cells desensitized rapidly to mechanical stimulation.[38,44] Burr et al.[38] reported in animal studies that a recovery period of 4-8 hours between osteogenic stimulus is sufficient to completely reestablish a full mechanically sensitive state in bone. Robling et al[44] also found that mechanical loading activities are more osteogenic if the load cycles are applied in discrete bouts, separated by several recovery periods, than if the loads are applied in a single session.

A. Exercise Training and Estrogen Levels on Bone Health in Adolescent Girls and Women.

In terms of bone health in women, the reported mechanisms for estrogen effect on bone are

1) estrogen plays an important role in the mechanical adaptation to loading in young women, Particularly prior to the end of puberty,
2) estrogen acts directly via suppression of osteocyte receptors that activate osteoclastic activity, and
3) estrogen has an anti-oxidant effect on Osteocytes.[14,46]

Estrogen deficiency promotes osteoclastogenesis and accelerating bone resorption. Thus, osteoporosis affects post menopausal women because of the suppression or absence of estrogen production.

In adolescent girls during menarche, their skeleton's ability to adapt to mechanical loading via physical activity or exercise training is greatly enhanced when estrogen levels are high.[15] It has been reported that estrogen deficiency in older postmenopausal women aged 70-80 years tend to have lower trabecular and cortical BMD, cortical thickness, and Stress Strain Indexes (mm^3) compared to younger post menopausal women, age 48-69 years.[15] This is why osteoporosis affects older women more than premenopausal women, younger postmenopausal women and men.

The positive impact of physical activity and peripubertal estrogen level on bone cross-sectional geometry and strength have been reported in children[14] and osteoporotic women.[46] For example, physically active adolescent girls who have higher estrogen levels during the first menarche and begin strenuous exercise or sport training prior to menarche gain twice as much bone mineral content (BMC) as do girls who begin after puberty.[14]

Physical activity or exercise training is recognized as one of the most important lifestyle strategies to maximize peak bone mass during growth.[47,48] Furthermore, skeletal response to different types of physical activity or exercise training is highly dependent on the nature of musculoskeletal loads imposed, especially the magnitude and rate of strain.[38] It has been reported that both gravity-derived loads (i.e., impact training) and muscle-derived loads (i.e., resistance training) have produced positive effects on bone in young adults and premenopausal women.[38,48-51]

Influence of Age on Bone Mineral Parameters–Effects of Lean Mass and Fat Mass

It is unclear as to how body composition (i.e., fat mass and lean mass) influences bone development in boys and girls. During adolescence lean mass is one of the best determinants of bone mass throughout life.[52] Sayers and Tobias (2010) studied 4,005 boys and girls, mean age of

15.5 years, using dual-energy X-ray absorptiometry (DXA) to determine total body fat mass (FM) and lean mass (LM), as well as peripheral quantitative computed tomography (pQCT) to measure cortical bone mass at the mid-tibia. From the study, Sayers and Tobias[52] reported that in girls FM exerted a positive influence on bone mass, however, in boys LM stimulated greater cortical bone mass development, and conclude that FM in girls has a greater tendency to stimulate periosteal growth and suppress endosteal expansion. In summary, this study shows that excessive reduction in FM in girls could have adverse effects on the developing skeleton leading to an increased risk of osteoporosis in later life[52] Wilkinson et al. [53] studied physically active young boys (aged 12-14 years) to determine whether FM or LM is a stronger predictor of BMD and hip geometry estimates and reported that

1) total body BMD was significantly correlated with LM but not FM, and
2) FM, after accounting for height, age, moderate-to-vigorous physical activity and LM had no significant relationship with BMD or hip geometry, except for arms BMD. The take-home message from these two studies are that LM, not FM, is the stronger predictor of BMD and hip geometry estimates in physically active boys as well as in girls.[52,53]

Regarding the effect of childhood vigorous physical activity and bone health, Christoffersen et al.[7] studied the association between childhood fractures, physical activity levels and bone mineral parameters during adolescence aged 15-18 years and reported that there is a negative association between childhood fractures and BMD or bone mineral content (BMC) in adolescent girls reporting low physical activity levels. However, in boys the negative association appears only in vigorously active participations with a previous history of forearm fractures. [7] The take home message from this study is that there is a link between fore arm fractures and higher bone mineral parameters when engaging in moderate and/or vigorous physical activity in adolescence boys.[7]

Peak bone mass is attained during the second and third decades of life.[54] However, there are a number of modifiable risk factors that can be used to predict low peak bone mass in young adult women. The use of body weight, height, and body mass index (BMI) for predicting fracture risk has been supported. For example, Ho and Kung[55] studied 418 premenopausal women, aged 20-39 years, and used measurement of DXA-BMDZ- score>_-1 standard deviation (SD) below the lumbar spine or total hip to serve as the criteria for low bone mass. The study results showed that

1) low body weight (<44kg) was associated with an 8.3-fold and 6.8-fold risk of having low BMD at the lumbar spine and hip, respectively, and
2) a body height ≤153 cm was associated with a 4.8-fold increased risk of having low BMD in the lumbar spine area and a 3.9-fold increased risk of having low BMD in femoral neck.[55] In addition, Ho and Kung[55] confirmed that

1) delayed puberty, determined by the onset of menstruation beyond 14 years of age, was associated with a 2.2-fold increased risk of having low BMD at the hip,
2) physical inactivity was associated with a 2.8-fold and 3.3-fold increased risk of having low lumbar spine BMD and low hip BMD, respectively, and
3) pregnancy protected against low lumbar spine BMD and low femoral neck BMD. The take home message from this study is that to maximize peak bone mass and lower the risk of fragility fractures in later life one may maintain an ideal body weight and engage in physical activity.[55,56]

In a retrospective cohort study of 8,254 adult women, aged 40–59 years, Morin et al.[57] examined the associations with weight, BMI, DXA-BMD, and subsequent fractures with a 3.3-year follow-up. The study results showed that

1) women having one or more fractures in the 3.3 years follow-up period had femoral neck T-score ≥ −2.5 standard deviation (SD) below the young healthy adults BMD,
2) after adjustment for age, each SD decrease in weight was associated with a 19% increase in the risk of incident fracture, and
3) femoral neck BMD level and the presence of prevalent fractures were also associated with the risk of incident fractures. Morin et al.[57] concluded that BMI and weight were found to be negatively associated with fracture risk. For prevention of osteoporosis and incident fracture, premenopausal women who are sedentary should be reminded about the negative impact of low body weight or BMI on bone health.[56,57]

In women over the age of 65 with post menopause, body weight is positively associated with BMD. For example, in a large meta-analysis of 12 prospective population-based cohorts, DeLaet et al.[58] and Bonnick[23] reported that the age-adjusted risk of a hip fracture was increased 2-fold in older women with a BMI at or below 20 kg/m ^{2}, compared with older women with a BMI at or above 25 kg/m ^{2}. Also, Väänänen et al.[9] reported that women aged 65 years and older in the lowest quartile for weight had twice as many hip, vertebral and forearm fractures as those in the other quartiles.

Exercise Training Modalities on Bone Health

Consistently researchers have found that high level exercise training in terms of duration, frequency and impact-loading modalities all are associated with bone geometry and strength.[44,48,59,60] The benefits of exercise training on bone health and the negative impact of space travel and bed rest on bone have been the focus of scientific research since the 1980s.[47,61-69] On the negative impact of space travel on bone, it has been reported that bone loss and calcium balance during extended space flights of astronauts and cosmonauts occurred after 28-,59- and 84-day space flight missions. This study reported that the mean calcium and phosphorus balance fell from positive balances before flight to negative values during flight, then returned to positive after flight.[70] Note that the increase in calcium ions in the blood triggers a reduction in parathyroid hormone secretion and a subsequent calcium excretion in the urine.[70]

The effectiveness of musculoskeletal loading activities for improving and maintaining bone integrity has yet to be defined. This is because exercise training parameters influencing bone resorption and formation include the type (or mode), frequency, intensity and duration of the mechanical stimulus.[51,59,71-73] For example, Robling et al.[44] reported that bone quality and bending strength can be improved if the mechanical stimulus is induced by short increments rather than over long periods. The consensus among bone researchers as to the potential osteogenic exercise regimens include

1) impact-load activities should be at high magnitude and low repetitions,
2) long-term mechanical loading should be separated into short bouts of work-rest intervals, and
3) the strain or load imposed on the skeleton should be distributed throughout the bone structure, involving multiple directions and be progressive in nature.[44,51,59]

For example, synchronized swimmers practiced in the water vigorously moving and sculling their arms as well as kicking and treading water with their legs to quickly (or slowly) propel their body upward, sideward or backward to perform various artistic movements in the water. These well-trained female synchronized swimmers were reported to have similar high ulnar and tibial bending strength and high wrist and calcaneus BMD compared to well-trained female gymnasts. [71] It should be noted that swimming (i.e., a non-impact loading exercise) does not seem to negatively affect bone mass, although it may not be one of the best modes of exercise to be practiced in order to promote bone strength and BMD.[72] Resistance training was repeatedly recommended for use as one of the training modalities for promoting bone strength and BMD in sedentary young and older women.[49,50,59,74,75]

Kelley at al.[76] reported that on an average, exercise training results in small but significant gain in femoral neck (FN) and lumbar spine (LS) BMD in premenopausal women. While the exercise-induced benefits observed for FN and LS BMD were statistically significant, their clinical relevancy of such changes is not known because of the limitations of DXA-derived BMD that does not account for other aspects of bone quality such as micro architecture (i.e., bone strength).[67,77] There is a clear clinical need to improve the diagnosis of osteoporosis. The improved diagnosis of those at risk for fracture will permit better targeting of intentions to prevent fragility fractures especially when DXA-BMD has been shown to have relatively poor discriminatory accuracy to distinguish individuals who will fracture from those will not(i.e., the use of BMD T-score< -2.5).[77-79] Vainionpää et al.[48] studied the effect of impact exercise and its intensity on bone geometry at weight-bearing tibia and femur in premenopausal women and found that exercise training has no significant effect at the proximal tibia and femoral shaft. However, after the bone outcomes analysis excluded those with low exercise compliance the authors found that greater compliance was associated with significant gain in BMD ranging from 0.5% to 2.5% at the proximate tibia. In summary, a well-designed exercise training study should address both exercise training compliance and bone outcomes assessment technology.[48,71,74,76,78,79]

In term of resistance training, Kelley et al.[76] suggest that greater increases in FN BMD were associated with a greater number of sets used for resistance training and that a higher % 1RM weights used in resistance training is needed to increase FN BMD in premenopausal women. Liang et al.[81] speculated that in untrained young women their FN BMD may be close to or at their peak BMD level and any further increase in BMD with resistance training might be small. Thus, Lianget al.[81] suggest that higher % of 1RM weights(i.e., $\geq$80%1RM) should be applied as the training intensity. Note that significant increases in both upper and lower body strength can be observed in resistance training in premenopausal and postmenopausal women.[74,76,81,82]

It should be noted that intensity of exercise that induces changes in BMD is site-specific and the optimal intensity for inducing osteogenic responses may vary between different skeletal sites.[59] Resistance training combined with aerobic exercise and neuromuscular training may be prescribed for individuals to increase bone strength and BMD because these multi-mode training regimens provide cardiorespiratory, musculoskeletal and neuromotor adaptations for improving cardio respiratory fitness and muscle strength and endurance.[50,60] In sports training/competition, this type of multi-modal activity is represented in sporting activities such as soccer, volleyball, tennis, badminton, gymnastic, basketball, hurdling, synchronized swimming, etc.[51,59] For physically inactive older men or women, whole-body vibration training appears to be superior to strength training, aerobic exercise or the combination of strength and aerobic exercise for improving BMD.[60]

Exercise Training Studies on Bone Health and Bone Mineral Density.

Lambert et al.[83] recruited 148 sedentary overweight women, aged 25 to 44 years to study the effect of resistance training (n=72) or non-exercise (n=76) on bone mineral density (BMD) and content (BMC) in the femoral neck (FN) and lumbar spine (LS) for 2 years. FN and LSBMC and BMD were measured by dual-energy X-ray absorptiometry (DXA). The authors found that Resistance training had no effect on FN and LS BMD.[83] Lambert et al[83] speculated that resistance training may have influenced bone size and recommended that research should also include assessing changes in bone dimensions and geometry with resistance training in premenopausal women. Lambert et al.[83] recruited physically active healthy young women (aged18-30years) to study the effect of high-impact loading and high-intensity resistance training on upper and lower limbs for 10 months, twice weekly on BMD (i.e., DXA), indices of bone strength (i.e.,pQCT-derived measures) and bone quality (i.e.,QUS-derived measures). The study results showed that 1) high-impact loading exercise training improved distal QCT-derived BMD of the upper limb and lower limb more than high-intensity resistance training, 2) high-impact loading exercise training improved upper limb bone strength index more than high-intensity resistance training, and 3) high-intensity resistance training improved DXA-derived cortical volumetric BMD at the femoral neck more than high-impact loading exercise training. Lambert et al.[83] concluded that high-impact exercise training and high-intensity resistance training provide different site-specific effects in both upper and lower limbs, with superior osteogenic response observed at the distal segment from high-impact loading exercise training, while high-impact resistance training appeared to have greater effect on the shaft of the bone in young adult women. Dutto et al.[50] recruited healthy young women (aged 20-35 years) to study tibial bend strength and lower body BMD using two different modes of exercise that provided lower body high-impact training (step-hop aerobic exercise) or lower body muscular strength training. These healthy young women were randomly assigned to step-hop aerobics exercise, lower body resistance training 3 times a week for 26 weeks or to a non-exercise control group. All participants were not physically trained, had a normal menstrual cycle, and were given 1500mg daily calcium supplement for 6 months. The study measurements include tibial and ulnar bending strength.[71, 84] and dual-energy x-ray absorptiometry (DXA) assessed BMD for the heel, wrist, lumbar spine L1-L4, and trochanter and the hip. The study results showed that changes in lower body BMD of the heel from base line to 6-months were significantly greater in the women with step-hop aerobics exercise (3.7%) than in the group with lower body resistance training (-0.6%). There were also significant increases in BMD at the lumbar L1-L4 (0.8%) relative to the resistance training group (-0.6%). However, in the step-hop aerobics group a loss of 0.6% in trochanter BMD compared to the resistance training group (a gain of 1.6%). There were also statistically significant decreased in hip BMD in the aerobics group (-1.3%) compared to the strength training group (0.4%). Changes in bone bending strength (Nm^2) between the two groups in the tibia or ulna were not observed after 6 months of exercise training. In all participants their tibial bending strength remained unchanged. Dutto et al.[50] concluded that in healthy premenopausal women 3 days a week of high-impact aerobics exercise for 6 months significantly enhance BMD in the leg, heel, and the lumbar L1-L4 spine, but did not enhance tibial bending strength. The implications for the prevention of osteoporosis later in life are that 1) young healthy women's spine and heel BMD can be increased up to3.6% with 45-50 min of high-impact aerobic exercise 3 times a week for 26 weeks and cannot be improved with lower body resistance training, and 2) activities for daily living and sedentary life-style resulted in no change in spine or leg BMD. In another study conducted by Miller et al.[74] who studied healthy young women, aged 18-26 years, to perform concentric (CON) or eccentric (ECC) iso kinetic resistance training with the non dominant limb three times a week for 20 weeks. Tibial bending strength was assessed.[71,84] and tibial BMD were scanned using DXA at pre-test and post-test on both limbs. The study results showed that both resistance training groups significantly increased tibial *EI* in the CON and ECC groups compared to the untrained tibial. Tibial BMD increased in both trained and untrained tibiae, with no significant difference between limbs.[74] Zhang et al.[85] systematically reviewed and compared the efficacy of different modes of exercise interventions on BMD in middle-aged and older patients with osteoporosis and osteopenia. The study outcome was BMD of different parts of the body. The study results showed that 1) combined exercise, resistance training, aerobic exercise and mind-body exercise had a significant positive effect on lumbar spine BMD, 2) all modes of exercise intervention significantly increased femoral neck BMD compared with no exercise, and 3) both aerobic exercise and resistance training improve total hip BMD with resistance training ranked the highest.[85]

Sports Participation/competition on Bone Health and Mineral Density.

Sport participations and/ or competitions during the years when peak bone mass is being acquired may lead to adaptive changes that improve bone architecture and material property through increased bone mass and enhanced geometric properties. This is because peak bone mass is attained before and during the first decade of life.[19,20] Tenforde and Fredericson[54] reported that high-impact loading and odd-impact sports participation in young female athletes, age10-30 years, are associated with higher bone mineral content (BMC), BMD, and enhanced bone geometry in anatomic regions specific to the loading patterns of both high-impact and odd-impact loading sports. In their study, the types of high- impact loading sports include gymnastics, hurdling, judo, karate, volleyball, and other jumping sports. Tenforde and Fredericson[54] classified odd-impact loading sports as soccer, basket ball, racquet games, step-aerobics, and speed skating sports. The authors conclude that continued participation in

1) sports training may retain some benefits of increased BMD,
2) repetitive low-impact sports such as distance running are associated with favorable changes in BMC or BMD, and
3) non-impact sports such as swimming, water polo, and cycling are not associated with improvements in BMC or BMD.[54] Note that the authors also reported that female adolescent distance running was associated with suppressed bone mineral accrual.[54]

Rocha-Rangel et al.[51] conducted a study to determine whether sports training comprised of high-impact loading sport i.e., volleyball (VOL), odd impact loading sport i.e., soccer (SOC), and low impact sport i.e., long-distance running (RUN) were associated with tibial and ulnar bending strength and calcaneus and wrist BMD in young female athletes. Tibial and ulnar bending strength (*EI,* Nm^2) were assessed using a mechanical response tissue analyzer (MRTA). Calcaneus and wrist BMD (g/cm^2) were assessed using a peripheral dual-energy X-ray absorptiometry (DXA). The results showed that 1) tibial *EI* of VOL and SOC were significantly greater compared to the non-athletes, but not different between athletic groups, and 2) ulnar *EI* of SOC was significantly higher than the non-athletes. Calcaneus BMD of VOL, SOC, and RUN were significantly higher than non-athletes but not different between athletic groups. Wrist BMD of VOL and SOC were significantly higher than non-athletes. Roche-Rengel et al.[51] conclude that female VOL athletes exhibit greater tibial bending strength than RUN and non-athletes, but not greater than SOC. Also, female SOC athletes exhibit significantly greater ulnar bending strength and wrist BMD than non-athletes, but not VOL athletes.

In another study conducted by Nordström et al.[86] who reported that in young male badminton and ice hockey players after two years of follow-up with these athletes and found that the gains in BMD and BMC of the femoral neck and in BMC of the humerus were significantly higher in badminton players compared with the control group, and that the badminton players also gained greater hip BMC and hip area compared with the ice hockey players. However, after adjustment for body weight, the badminton players still had higher hip BMD and BMC, femoral neck BMC, and humeral BMC compared with the ice hockey players at the follow-up. From this study, Nordström et al.[86] conclude that 1) badminton sport is associated with higher gains in bone mass and size compared with ice hockey after puberty in men and 2) the differences between the two sports might be associated with higher strains on the bones from badminton training and competition.

Nikander et al.[59] conducted a study of female athletes to assess whether musculoskeletal loading-related differences in bone structure are associated with loading type or the muscle performance-related joint moments. In a study of 113 females national level athletes, Nikander et al.[59] measured the athletes' weight-bearing skeleton at shaft sites of the tibia, radius and humerus, and at distal sites of the tibia and radius using peripheral quantitative computed tomography (pQCT).
Note that for the weight-bearing lower extremities, the loading modalities were classified into

1) high-impact loading (hurdling, volleyball),
2) odd-impact loading (soccer, racket-sports) and
3) repetitive, nonimpact loading (swimming).

For the non-weight bearing upper extremities the loading modalities were classified into

1) high magnitude loading (functional weightlifting in hurdling and soccer),
2) impact loading (volleyball, racket-sports) and
3) repetitive, nonimpact loading (swimming).

Results of the study showed that the athletes' bone mass was substantially higher at loaded bone sites compared with the non athletic females.

The authors conclude that

1) at the weight-bearing lower extremity, the strong bone structure of the female athletes was attributable to muscle performance-related joint moments and impact loading modality, and
2) at the bone shaft sites of the non-weight-bearing upper extremity, the strong bone structure was mainly attributable to the joint moments.

Therefore, different musculoskeletal loading history and other features of loading seemed to govern the skeletal adaptation at the upper and lower extremity.[59] The take home messages are that musculoskeletal loading of the female athletes' bone appears to be able to build mechanically strong and appropriate bone structures in addition to bone mass. The weight- bearing bone structures of the female athletes were characterized by larger diaphysis, thicker cortices and denser trabecular bone.[59] Another bone health study in endurance athletes involving runners, cyclists and swimmers was reported by Scofield and Hecht.[87] The authors conclude from the study that adolescents and adults who participate in endurance sports such as running, and non-weight-bearing sports such as cycling and swimming often have lower BMD than athletes participating in ball and power sports. In another study by Rector et al.[88] on non-weight bearing sports such as road cycling and road running on bone health in adult male recreational athletes. The non-weight bearing athletes (i.e., cyclists) had significantly lower BMD of the whole body and spine compared with the weight-bearing athletes (i.e., runners) despite having similar age, weight, body mass index, body composition, hormonal status, current activity level, and nutrient intakes. Also 63% of the non-weight bearing athletes had osteopenia of the spine or hip, compared with 29% of weight-bearing athletes. The take home message from this study is that current bone loading is an important determinant of whole-body and lumbar spine BMD.[88]

Hagman et al.[89] studied BMD in females trained in lifelong team handball and young elite soccer athletes. The study results show that lifelong elderly team handball players had 1) higher BMD in all regions of the lumbar spine, and 2) higher BMD in the femoral Ward's triangle (9%) and trochanter (7%) of the left leg, compared to the elderly untrained control subjects. Furthermore, the lifelong elderly team handball players and young untrained control females had similar BMD in trochanter, lumbar spine 1-4, and mean leg despite an age difference of about 40 years. Young elite soccer athletes had higher BMD in all regions of the proximal femur (18-29%) and lumbar spine (12-16%) compared to young untrained control subjects. The authors conclude that lifelong team handball training and elite soccer training are associated with superior bone mineralization and changed bone turnover in elderly and young women.[89]

Non-Pharmacological and Supplements Use to Prevent Osteoporosis

Healthy lifestyle habits such as achieving a normal body weight, regular exercise, adequate calcium and vitamin D intake, tobacco cessation, and moderate alcohol consumption are important in preventing osteoporosis.[90] For example, calcium, a major component in bone structure, is not produced by the human body, and is only available from food or supplements. Vitamin D is equally important in bone health as it enhances the intestinal absorption of calcium. In fact, with adequate vitamin D, about 30 to 40% of dietary calcium can be absorbed as opposed to only 10 to 15% in a vitamin D deficient state.[91] To maximize peak bone mass in premenopausal women, the recommended daily intake for both nutrients are 1000 mg of calcium (1300 mg in 9 to 18 years old) and 600 international units (IU) of vitamin D[92] Slovik et al.[93] reported that daily subcutaneous injection of a 24 synthetic human parathyroid hormone combined with daily ingestion of 1,25$(OH)_2$ vitamin D significantly increased bone density in the spine in middle-aged men with idiopathic osteoporosis. These results indicate that increasing intestinal absorption of dietary calcium while simultaneously stimulating new bone formation with small doses of parathyroid hormone can restore spinal bone in osteoporotic men.[94] Note that dermal synthesis of vitamin D is also a major natural source of vitamin D, as brief casual exposure to natural sunlight can be equal to the ingestion of 200 IU.[95] Vitamin D and calcium supplements are not necessary if adequate intake of both nutrients can be achieved from diet. However, according to the 2020 data from US Department of Agriculture (USDA), the average daily intake of calcium and vitamin D for women over 20 years of age are inadequate at 842 mg and 152 IU, respectively. On the other hand, over consumption of calcium and vitamin D should be avoided as hypercalcemia can have adverse health effects including kidney stones and stomach ulcer. The tolerable upper limit for calcium supplement is 2500mg (3000mg for 9 to 18 years old) and for vitamin D is 4000IU.[92]

Conclusion

For the purpose of building strong bone or peak bone mass during the growing years as teenagers or young adults the recommended approach is to engage in regular exercise training and/or sports participation because musculoskeletal loading activities during exercise training and sports participation are relatively safe and without side effects especially when one begins to engage in regular exercise training at a younger age with club sports and continues the training activities to adulthood and old age with supervision by qualified professional trainers.

Non-pharmacological approach such as regular exercise training and adequate calcium and vitamin D supplements should be prescribed first to avoid the uncommon but serious adverse effects associated with pharmacological therapies as well as the high cost of the drugs.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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